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Research report

18-Methoxycoronaridine, a non-toxic *iboga* alkaloid congener: effects on morphine and cocaine self-administration and on mesolimbic dopamine release in rats

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Abstract

Ibogaine, a naturally occurring *iboga* alkaloid, has been claimed to be effective in treating addiction to opioids and stimulants, and has been reported to inhibit morphine and cocaine self-administration in rats. However, ibogaine also has acute nonspecific side effects (e.g. tremors, decreased motivated behavior in general) as well as neurotoxic effects (Purkinje cell loss) manifested in the vermis of the cerebellum. 18-Methoxycoronaridine (MC) is a novel, synthetic *iboga* alkaloid congener that mimics ibogaine's effects on drug self-administration without appearing to have ibogaine's other adverse effects. Acutely, in rats, MC decreased morphine and cocaine self-administration but did not affect bar-press responding for water. In some rats, treatment with MC (40 mg/kg) induced prolonged decreases in morphine or cocaine intake lasting several days or weeks. MC had no apparent tremorigenic effect, and there was no evidence of cerebellar toxicity after a high dose (100 mg/kg) of MC. Similar to the effects of ibogaine and other *iboga* alkaloids that inhibit drug self-administration, MC (40 mg/kg) decreased extracellular levels of dopamine in the nucleus accumbens. MC therefore appears to be a safer, ibogaine-like agent that might be useful in the treatment of addictive disorders.

Keywords: Ibogaine; *Iboga* alkaloid; 18-Methoxycoronaridine; Morphine; Cocaine; Drug self-administration

1. Introduction

Several alkaloids are found in the root bark of the African shrub *Tabernanthe iboga*. One of them, ibogaine, has been claimed, in two United States patents (number 4,499,096, Feb. 12, 1985 and number 4,587,243, May 6, 1986), to be effective in treating opiate (heroin) addiction and stimulant (cocaine and amphetamine) abuse, respectively. Treatment with ibogaine supposedly interferes with the 'physiological and psychological aspects' of addiction and abolishes craving for drugs. A single oral treatment of ibogaine or its salts in dosages of 6 to 19 mg/kg is claimed to be effective for about 6 months, while a series of four treatments may eliminate addictive behavior for approximately 3 years. Several studies [2,8,14,16,17,29,30] using animal models of addiction have provided at least

limited substantiation of these claims. For example, in our initial study [17], we reported that ibogaine dose-dependently decreased morphine self-administration in the hour after ibogaine treatment (acute effect) and, to a lesser but significant extent, a day later (aftereffect). In some rats there was a persistent decrease in morphine intake for several days or weeks after a single injection of ibogaine whereas other rats began to show such persistent changes after two or three weekly injections, and a few rats appeared to be entirely resistant to prolonged aftereffects. We [14] and others [2] have subsequently observed similar effects of ibogaine on cocaine self-administration in rats.

Ibogaine exhibits side effects that may limit its therapeutic utility. In addition to having stimulant and hallucinogenic properties, ibogaine induces tremors. In rats, the tremors are most commonly manifested as whole-body shaking, and appear to be due to activation of an olivocerebellar pathway [6,19,25]; high doses of ibogaine have been shown to produce damage to the cerebellar vermis in rats, presumably a result of overstimulation of cerebellar

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Purkinje cells [24,25]. Previous work with other *iboga* alkaloids has demonstrated that long-term (one day and longer) decreases in drug (morphine and cocaine) self-administration can be dissociated from acute tremorigenic activity; R-ibogamine and R-coronaridine, two non-tremorigenic *iboga* alkaloids, mimicked ibogaine's effects on drug self-administration. Thus it appears possible to develop safer ibogaine-like agents. But these non-tremorigenic alkaloids also mimicked ibogaine in terms of other nonspecific acute effects; that is, ibogaine, as well as R-ibogamine and R-coronaridine, inhibit responding for non-drug (e.g. water) as well as for drug reinforcers during the first 1–2 h after administration [17]. While this nonspecific depression induced by ibogaine initially appeared to be attributable to motor incoordination accompanying tremors [17], this now seems unlikely in view of the effects of R-ibogamine and R-coronaridine [14]. In the present report we describe the effects of 18-methoxycoronaridine (MC), a novel *iboga* alkaloid congener that mimics ibogaine's inhibitory effects on morphine and cocaine self-administration; however, MC is non-tremorigenic, produces no cerebellar neurotoxicity and, unlike several other previously tested *iboga* alkaloids, has no acute depressant effect on bar-press responding for water.

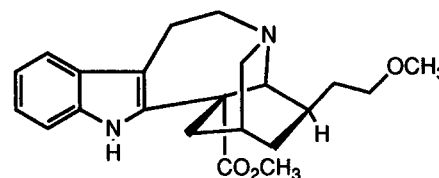
2. Materials and methods

2.1. Drug administration

Racemic MC hydrochloride was synthesized by Martin Kuehne and Upul Bandarage, University of Vermont, Burlington, VT. The structure of MC is shown in Fig. 1. The preparation and characterization data of MC are analogous to data previously described for the synthesis of coronaridine [1]. All injections were made intraperitoneally; doses are expressed as the hydrochloride salt. Different doses of MC (or saline) were administered to different groups of rats; rats were injected 15 min before a morphine or cocaine self-administration session. Drug injections were usually made on Wednesdays and, in some cases, repeated injections were made at weekly intervals.

2.2. Subjects and apparatus

The subjects were naive female Sprague–Dawley (Taconic, Germantown, NY) rats, approximately 3 months old and weighing 230–250 g at the beginning of the experiment; female rats were used because they grow at a much slower rate than males and are less likely than males to outgrow their intravenous cannulas. Rats were housed singly in Wammann hanging cages and maintained on a normal light/dark cycle (lights on/off at 0700 h/1900 h). All self-administration testing was conducted in twelve BRS/LVE operant test cages, each enclosed in a sound attenuated cubicle. Responses on either of two levers



18-methoxycoronaridine

Fig. 1. Structure of 18-methoxycoronaridine (MC).

(mounted 15 cm apart on the front wall of each test cage) were recorded on an IBM compatible 386 computer with a Med Associates, Inc. interface. The intravenous self-administration system consisted of polyethylene-silicone cannulas constructed according to the design of Weeks [34], BRS/LVE harnesses and commutators, and Harvard Apparatus infusion pumps (#55-2222).

2.3. Self-administration procedures

Shaping of the bar-press response was initially accomplished by training rats to bar-press for water. Cannulas were then implanted in the external jugular vein according to procedures described by Weeks [34]. Self-administration testing began with a single 24-h session followed by daily 1-h sessions, 5 days (Monday to Friday) a week; rats were tested about the same time each day, during the middle of the light cycle. Depending upon the group, a lever-press response produced either a 20 μ l (morphine) or 50 μ l (cocaine) infusion of drug solution (0.01 mg of morphine sulfate or 0.1 mg of cocaine hydrochloride) in about 0.2 (morphine) or 0.5 (cocaine) seconds. Since all rats generally weighed 250 ± 20 g, each response delivered approximately 0.04 mg/kg of morphine or 0.4 mg/kg of cocaine; these doses are about two to four times the threshold doses required for maintaining self-administration behavior [e.g. [8,10]]. One non-contingent drug infusion was administered at the beginning of each session. Experiments to assess the effects of MC were begun when baseline self-administration rates stabilized ($\leq 10\%$ variation from one day to the next across 5 days), usually after 2 weeks of testing. In order to provide an indication of the specificity of MC's effects on bar-pressing for morphine and cocaine, MC was also administered to other rats bar-pressing for water on a comparable schedule (continuous reinforcement; 1-h sessions).

2.4. Microdialysis and HPLC procedures

Under pentobarbital anesthesia, each rat (female Sprague–Dawley) was implanted stereotaxically with a guide cannula over the nucleus accumbens so that, when inserted, the tip of the dialysis probe would be located in the shell of the nucleus accumbens (rostral, +1.6 mm from bregma; lateral, ± 0.7 mm; ventral, -8.6 mm from the skull surface) [26]. Cannulas were fixed firmly in the

skull with dental cement. The side (left or right) of the brain implanted with a cannula was alternated from animal to animal.

At least 4 days after surgery, a rat was placed in a dialysis chamber, a cylindrical (30 cm diameter) Plexiglas cage providing free access to food and water. The probe (2 mm; CMA 8309562) was then lowered into the guide cannula. The dialysis probe was continuously perfused with a solution containing 146 mM NaCl, 2.7 mM KCl, 1.2 mM CaCl_2 , 1.0 mM MgCl_2 and 0.05 mM ascorbic acid at a flow rate of 1 $\mu\text{l}/\text{min}$. On the next morning (15–20 h later), the dialysis experiment was carried out on a freely moving animal. Twenty minute fractions were collected in vials containing 2 μl of 1.1 N perchloric acid solution (containing 5 mg/l EDTA and 5 mg/l sodium metabisulfite). Upon completion of an experiment, rats were killed and histological analysis of each brain was performed to verify the location of the probe.

Perfusate samples were analyzed by HPLC with electrochemical detection. The HPLC consisted of a Waters pump (model 510), a WISP autosampler (model 712), a Phase Separation Spherisorb C-18 column (S3 ODS2; 10 cm $\times$ 4.6 mm) and a Waters detector (model 464). The mobile phase consisted of 6.9 g/l sodium monobasic phosphate, 450 mg/l heptane sulfonic acid, 80 mg/l disodium EDTA, and 110 ml/l methanol; the solution was adjusted with HCl to pH 3.7 and was pumped at a rate of 1.2 ml/min. Chromatograms were processed using Hewlett-Packard HPLC 2D Chem Station software.

Previous work has demonstrated that dialysate concentrations of dopamine (DA) and DOPAC are highly correlated ($r \geq 0.9$) with extracellular levels of these compounds as determined in 'no net flux' studies [12]. Prior to use in vivo, in order to identify 'bad' probes [12], each probe was calibrated in vitro at room temperature in an artificial CSF solution gassed with argon and containing DA (15 pm/ml), DOPAC (1.5 nm/ml) and HVA (0.75 nm/ml). In vitro recoveries averaged 30–35% and probes having in vitro recoveries of less than 20% were not used in vivo.

2.5. Tremor assessment

Ibogaïne and several other *iboga* alkaloids elicit whole body tremors [e.g. [14]]. To assess this potential effect of MC, direct visual observations were made of rats confined in a Plexiglas cylindrical (9 inches in diameter) enclosure; videotapes were sometimes made so that initial observations could be confirmed at a later time. Tremors were rated as absent, moderate or intense on a minute to minute basis for 30 min, beginning 15 min after drug administration.

2.6. Evaluation of potential cerebellar toxicity

Rats received one injection (i.p.) of 100 mg/kg MC per day for either one or three consecutive days. They were

sacrificed one week later with an overdose of sodium pentobarbital and fixed, by cardiac perfusion, with 10% formalin. The brains were removed and cryo-protected in sugar formalin. The cerebella were then separated from the brainstem and cut, with a freezing microtome, in 30 μm -thick, coronal sections. These were collected in groups of five consecutive sections. One section per group was stained with cresyl violet to allow identification of the posterior end of the deep cerebellar nuclei.

As in earlier studies [5,23], procedure II of Fink and Heimer [9] was used to evaluate degeneration of cerebellar Purkinje cells. Tissue was selected for Fink-Heimer processing by using the set of five sections containing the posterior end of the deep cerebellar nuclei as the reference point. From this point, sections 900 μm apart (i.e. from every sixth set of five) that sampled the entire anterior-posterior extent of the cerebellum were used. This selection procedure insured that in every animal all cerebellar lobules were systematically sampled.

Coronal sections are cut nearly perpendicular to the largely two-dimensional Purkinje cells. As a result, a degenerating Purkinje cell in a Fink-Heimer stained, coronal section appears as a thin line of silver grains that extends through the molecular layer of the cerebellum [5]. In the present study, the presence or absence of silver grains was determined by examining the tissue with the light microscope.

The Fink-Heimer stain can be capricious. Therefore, control sections from a cerebellum previously shown to contain degeneration was processed along with sections from MC-treated animals. The degeneration in these control sections resulted from an injection of 100 mg/kg ibogaïne (i.p.). If degeneration was not apparent in the control sections, the Fink-Heimer procedure was repeated on another set of sections. A previous study [23] provided tissue from naive and saline-treated animals for comparison with that from MC-treated animals. Histological processing of the tissue followed the same procedures used in the present study.

3. Results

3.1. Drug self-administration

Fig. 2 shows the initial acute effects of MC on morphine and cocaine self-administration and on bar-pressing for water. MC produced a dose-related depression of morphine and cocaine intake (ANOVA, $P < 0.001$ in each case) but had no significant effect on bar-pressing for water. Fig. 3 shows that MC, 40 mg/kg, depressed morphine and cocaine intake for at least a day afterwards. In both cases, a group $\times$ days interaction was significant ($P < 0.05$ in a two-way ANOVA), and paired t -tests with baseline values were significant ($P < 0.05$ – 0.01) for days 1, 2 and 3 (morphine) or days 1 and 2 (cocaine) in the MC

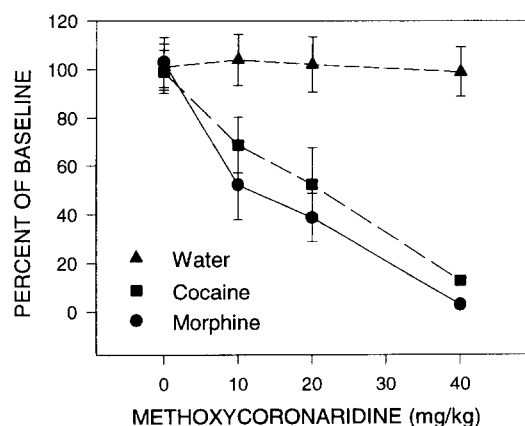


Fig. 2. Acute effects of MC on morphine and cocaine self-administration and on bar-pressing for water. Each data point is the mean ($\pm$ S.E.) from 4–8 rats. Baseline was calculated as the average rate for the three sessions preceding drug or saline (0 mg/kg) treatment. All doses of MC had significant effects (ANOVA and *t*-tests, $P < 0.05$ – 0.001) on morphine and cocaine self-administration but not on bar-pressing for water.

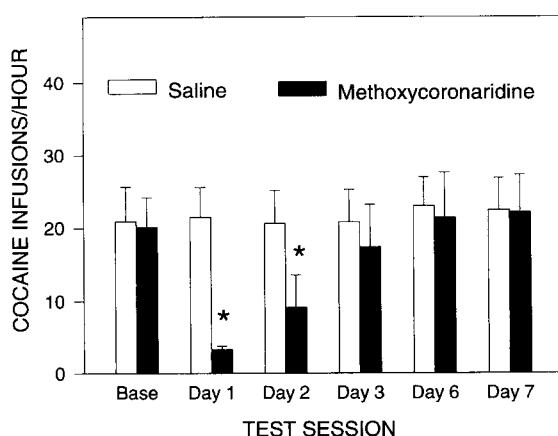
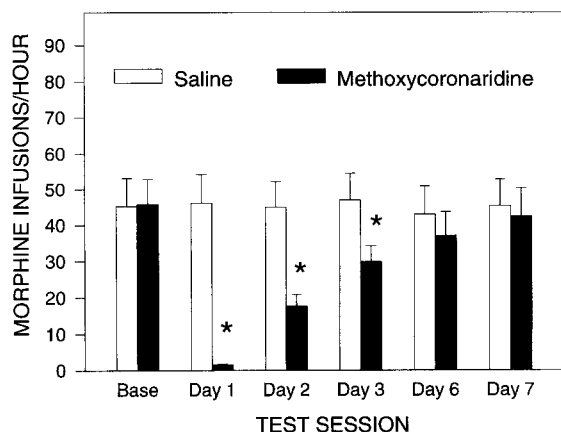


Fig. 3. Aftereffects of MC (40 mg/kg) on morphine and cocaine self-administration. Each data point is the mean ($\pm$ S.E.) from 6 rats. 'Base' refers to the baseline rate of responding, calculated as the average for the three sessions preceding drug or saline treatment. There were significant (ANOVA, $P < 0.05$) effects on Days 1 and 2 in both cases and on Day 3 in rats self-administering morphine (* = paired *t*-tests, $P < 0.05$ – 0.01).

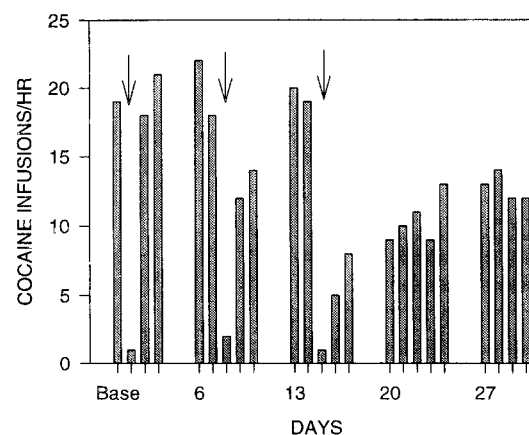
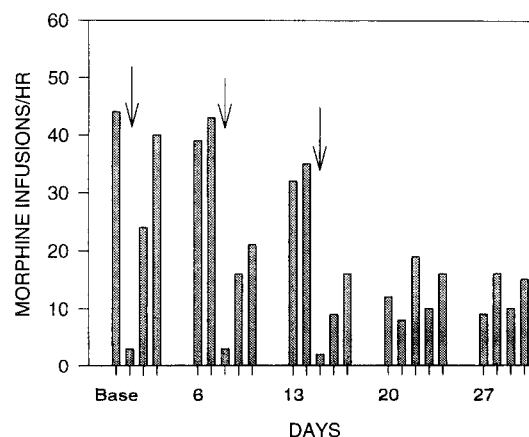


Fig. 4. Individual responses to repeated injections (indicated by arrows) of MC (40 mg/kg); in both cases, prolonged aftereffects only became apparent after the third injection.

treatment groups. The extent of these aftereffects (one or more days later) on drug self-administration varied substantially from rat to rat; responses beyond a day later (Day 2) ranged from no further effect to a prolonged depression of morphine (four of six rats) or cocaine (two of six rats) intake, lasting up to 3 weeks. In general, the aftereffects on cocaine intake were somewhat more variable than those on morphine intake. There was no significant aftereffect of MC on bar-press responding for water.

When prolonged aftereffects of a single dose of MC were not apparent for particular rats, repeated injections of MC, at weekly intervals, were made (this was done for two rats self-administering morphine and three rats self-administering cocaine). Fig. 4 shows examples of data from two rats that were administered MC three times: on the first two occasions there were only small effects beyond the day of injection whereas, after the third injection, morphine or cocaine intake was clearly depressed for at least several days afterwards. One morphine and one cocaine rat showed prolonged aftereffects following a second injection whereas one rat self-administering cocaine showed no aftereffects lasting more than a day even following three injections.

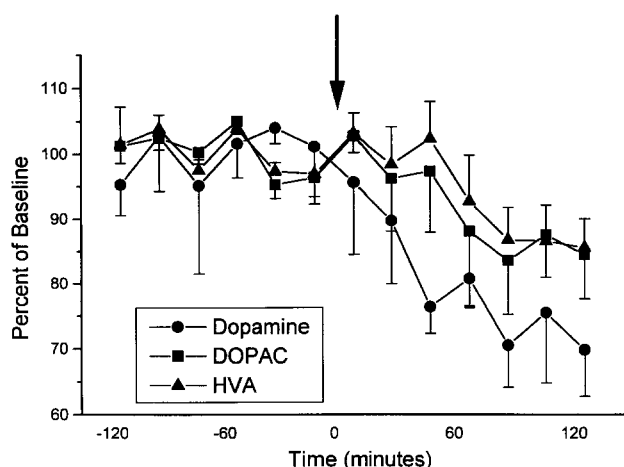


Fig. 5. Time course of extracellular dopamine, DOPAC and HVA levels in the nucleus accumbens after administration of MC (40 mg/kg, $N = 6$). Samples were collected at 20-min intervals. Data are expressed as a percent ($\pm$ S.E.) of baseline dialysate values. There were significant decreases in levels of all three substances (ANOVA, $p < 0.03$ – 0.002).

The Med Associates interface and software provided cumulative and event records of responding for each self-administration test session. For both morphine and cocaine, normal patterns of responding were characterized by an initial burst of drug intake at the beginning of each session followed by regularly spaced responding thereafter. Two kinds of MC-induced effects, very similar to those produced by ibogaine and other *iboga* alkaloids [14], were clearly apparent. Acutely, on the day of administration, the dose-related depressions of morphine and cocaine intake were characterized by complete suppression of responding early in a session followed by irregularly spaced and sporadic responding thereafter; the 40 mg/kg dose of MC suppressed responding almost entirely in most animals. In contrast, the prolonged aftereffects of MC on morphine and cocaine intake were characterized by quite normal patterns of responding; that is, although responding was depressed, the effects were distributed uniformly throughout a test session such that the initial burst in responding was shorter and subsequent responses were more widely spaced than during baseline conditions.

3.2. *In vivo* microdialysis

Fig. 5 shows the acute effects of MC on extracellular levels of DA, DOPAC and HVA in the nucleus accumbens (NAC). MC significantly (ANOVA) decreased DA ($P < 0.01$), DOPAC ($P < 0.03$) and HVA ($P < 0.002$).

3.3. Tremorigenic effects

Visual observations and videotape recordings of MC-treated (40 mg/kg) rats indicated very little if any tremorigenic activity. Ibogaine (40 mg/kg) and saline (1 ml/kg) were used as positive and negative controls, respectively.

MC could not be distinguished from saline. Even the rats treated with a high dose (100 mg/kg) of MC, used in the toxicity studies (below), had no apparent tremors.

3.4. Cerebellar toxicity

Data were collected from four animals treated with a single dose of MC and three animals treated with three doses. In tissue from all of the MC-treated animals, isolated, single lines of silver grains were found. These were identical to those found in tissue from naive and saline-treated animals [see refs. [5] and [23]]. Each line apparently represents a single, isolated degenerating Purkinje cell.

In marked contrast, every section from the animal given a high dose of ibogaine contained two or more broad bands of degeneration. As described previously [20,22], each band appeared to represent a group of up to ten adjacent, degenerating Purkinje cells. None of the sections from MC-treated animals displayed such bands. Because tissue from the ibogaine-treated animal was processed simultaneously with that from the MC-treated animals, the absence of bands of degeneration could not be due to procedural variability. It can be concluded that even multiple, high doses of MC failed to produce any evidence of degeneration above that normally seen in cerebellar tissue.

4. Discussion

MC (10–40 mg/kg) produced acute, dose-dependent reductions in both morphine and cocaine self-administration without disrupting bar-press responding for water. The specificity of this result is highlighted by the fact that ibogaine [17], as well as other *iboga* alkaloids [14] previously tested in this laboratory under identical conditions, all produced an acute inhibition of responding for water as well as for morphine and cocaine. MC (40 mg/kg) also had no apparent tremorigenic effect, and a high dose (100 mg/kg) of MC produced no evidence of any cerebellar toxicity. MC therefore appears to have an acute efficacy on morphine and cocaine self-administration that is comparable to the efficacy of ibogaine [14,17] but without having the latter's nonspecific and toxic side effects.

The aftereffects of MC were similar to those of ibogaine [14,17] and some other *iboga* alkaloids [14]. Long-term decreases in morphine or cocaine intake lasting for several days and in a few cases for several weeks after MC treatment occurred in some rats. It was not possible to predict which rats would respond in this way. When MC treatments were repeated at weekly intervals, most rats that were initially resistant began to show long-term aftereffects; only one rat self-administering cocaine failed to show prolonged effects after 3 weekly injections of MC.

In previous studies [14,20], acute administration of ibogaine and some other *iboga* alkaloids decreased extracellu-

lar levels of DA in the NAC. Only those *iboga* alkaloids that had significant aftereffects on drug self-administration significantly decreased DA in the NAC. The present results with MC are consistent with this relationship: MC decreased extracellular levels of DA in the NAC and had significant aftereffects on drug self-administration. It remains unclear, however, exactly how an acute change in extracellular DA levels can be associated with or responsible for a persistent behavioral effect. Perhaps a decrease in DA release is the first step in a sequence of neurochemical changes that directly mediates a prolonged change in drug self-administration behavior. Interestingly, MC decreased extracellular levels of the dopamine metabolites (DOPAC and HVA) in contrast to the increases previously observed with ibogaine [20]. Ibogaine has been shown to be a non-selective agent interacting with opioid, serotonin, NMDA, sigma and muscarinic receptors as well as amine uptake sites [4,21,22,29,31]. MC might be expected to have a somewhat different binding profile, perhaps lacking an affinity for NMDA receptors. Like ibogaine [20], MK-801, an NMDA antagonist, has been reported to increase HVA levels in cortex and striatum [3]. Although some investigators [22,28] have speculated that the interaction of ibogaine with NMDA receptors plays a major role in mediating its putative anti-addictive properties, other investigators [25,31] have implicated such a mechanism in ibogaine's known neurotoxic effects, of which MC is devoid.

In accordance with previous data [14], the results of the present study clearly show that *iboga* alkaloid effects on drug self-administration can be dissociated from neurotoxic effects involving the cerebellum. That is, it had been proposed by Molliver [33] that ibogaine-induced cerebellar damage might be responsible for its putative anti-addictive effects. However, we [14] subsequently showed that harmaline, which produces very similar cerebellar damage, had no persistent effects on either morphine or cocaine self-administration. Conversely, in the present study, we report that MC, which does have ibogaine-like persistent effects on drug self-administration, does not produce cerebellar damage.

Assuming that treatment with MC alters the reinforcing efficacies of morphine and cocaine, the treatment-induced decreases in morphine and cocaine intake could result from either antagonism or enhancement of morphine's and cocaine's actions [e.g. [15]]. That is, if MC antagonized a self-administered drug's actions, it would be expected that rats might transiently self-administer more drug in an attempt to compensate for the reduced effect but then self-administer less drug as extinction occurred (i.e. analogous to decreasing the drug infusion dose to below threshold); if MC enhanced a self-administered drug's actions, it would be expected that rats would also self-administer less drug but, in this case, as a way of compensating for the increased effect (i.e. analogous to increasing the drug infusion dose). The observed response patterns underlying

the alkaloid-induced aftereffects favor the latter interpretation, inasmuch as there was no evidence of a biphasic extinction pattern of responding that would support the 'antagonist' interpretation. Furthermore, preliminary results with other morphine and cocaine infusion dosages (0.08 and 0.8 mg/kg/infusion, respectively) indicate that MC produces downward shifts in the self-administration dose-response curves, consistent with the view that MC increases sensitivity to the self-administered drugs [e.g. [32]].

The mechanism underlying the aftereffects of MC is unknown although several possibilities have been suggested regarding ibogaine. One possibility is that *iboga* alkaloids, and *iboga* alkaloid congeners, may persist in the body for long periods of time. In an early study using spectrofluorometry [7], the half-life of ibogaine in rodents was reported to be about one hour, and ibogaine levels in the body were undetectable a day after its administration. However, more recently, using gas chromatography mass spectrometry, ibogaine has been detected a day after its administration in rat plasma and brain [10]; and other data indicate that the latter concentrations may be pharmacologically active [18]. We initially postulated that ibogaine might have an active and persistent metabolite [17,20]. Recent evidence has supported this idea. Noribogaine, which is probably ibogaine's primary metabolite [21], appears to persist in plasma for a prolonged period of time (i.e. at least 24 h) [21] and has several biochemical actions shared by ibogaine, including binding to kappa opioid [27] and NMDA [22] receptors. Further investigations will determine whether similar mechanisms are involved in MC's actions [11,13].

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